Claims

1. A method for diagnosing a disorder associated with altered β-secretase and/or γ-secretase processing of substrates, comprising

measuring the stability of a secretase pathway associated protein in a biological sample from a subject, wherein increased protein stability relative to that in a control biological sample is an indication that the subject has a disorder associated with altered β-secretase and/or γ-secretase processing of substrates.

2. The method of claim 1, wherein the disorder associated with altered β-secretase and/or γ-secretase processing of substrates is an Aβ-accumulation-associated disorder.

3. The method of claim 1, wherein the disorder associated with altered β-secretase and/or γ-secretase processing of substrates is selected from the group consisting of cancer, neurological diseases, immunologic diseases and glycoconjugate metabolism disorders.

4. The method of claim 2, wherein the Aβ-accumulation-associated disorder is selected from the group consisting of Alzheimer's disease, Down's syndrome, cerebrovascular amyloidosis, inclusion body myositis and hereditary inclusion body myopathies, diseases associated with abnormal BACE and/or γ-secretase activity, ischemia, oxidative stress, head trauma, stroke, hypoglycemia, and any neurodegenerative disorder with increased caspase activation.

5. The method of claim 1, wherein the secretase pathway associated protein is selected from the group consisting of: presenilins, nicastrin/Aph2, BACE, Aph1a, and Pen-2 protein.

6. The method of claim 5, wherein the presenilin is presenilin 1.

7. The method of claim 1, wherein the subject is human.

8. The method of claim 1, wherein the subject is at risk of developing Alzheimer's disease.

9. The method of claim 1, wherein the biological sample is selected from the group consisting of cells and tissues.

10. The method of claim 9, wherein the cells are neuronal cells.

11. The method of claim 9, wherein the tissue comprises neuronal cells.

12. A method for determining onset, progression, or regression, of a disorder associated with altered β-secretase and/or γ-secretase processing of substrates in a subject, comprising:

measuring the stability of a secretase pathway associated protein in a first biological sample of a subject,

measuring the stability of the secretase pathway associated protein in a second biological sample of a subject obtained at a second time,

comparing the measurement of stability in the first sample to the measurement of stability in the second sample as a determination of the onset, progression, or regression of the disorder associated with altered β-secretase and/or γ-secretase processing of substrates.

13. The method of claim 12, wherein the disorder associated with altered β-secretase and/or γ-secretase processing of substrates is an Aβ-accumulation-associated disorder.

14. The method of claim 12, wherein the disorder associated with altered β-secretase and/or γ-secretase processing of substrates is selected from the group consisting of cancer, neurological diseases, immunologic diseases and glycoconjugate metabolism disorders.

15. The method of claim 13, wherein the Aβ-accumulation-associated disorder is selected from the group consisting of Alzheimer's disease, Down's syndrome, cerebrovascular amyloidosis, inclusion body myositis and hereditary inclusion body myopathies, diseases associated with abnormal BACE and/or γ-secretase activity, ischemia, oxidative stress, head trauma, stroke, hypoglycemia, and any neurodegenerative disorder with increased caspase activation.

16. The method of claim 12, wherein the secretase pathway associated protein is selected from the group consisting of: presenilins, nicastrin/Aph2, BACE, Aph1a, and Pen-2 protein.

17. The method of claim 16, wherein the presenilin is presenilin 1.

18. The method of claim 12, wherein the subject is human.

19. The method of claim 12, wherein the subject has been diagnosed with Alzheimer's disease or is at risk of developing Alzheimer's disease.

20. The method of claim 12, wherein the biological sample is selected from the group consisting of cells and tissues.

21. The method of claim 20, wherein the cells are neuronal cells.

22. The method of claim 20, wherein the tissue comprises neuronal cells.

23. A method for identifying compounds that modulate caspase activation-induced stabilization of a secretase pathway associated protein comprising

contacting cells that have been induced to undergo caspase activation with a candidate modulator of secretase pathway associated protein stabilization, and

measuring the stability of the secretase pathway associated protein, wherein a difference in the stability of the protein relative to the stability of the protein in untreated cells is an indication that the candidate modulator is a compound that modulates the caspase activation-induced stability of the secretase pathway associated protein.

24. The method of claim 23, wherein an increase in the stability of the protein relative to the stability of the protein in untreated cells indicates the candidate modulator is an inhibitor of stability of the secretase pathway associated protein.

25. The method of claim 23, wherein a decrease of the protein relative to the stability of the protein in untreated cells indicates the candidate modulator is an enhancer of stability of the secretase pathway associated protein.

26. The method of claim 23, wherein the secretase pathway associated protein is selected from the group consisting of: presenilins, nicastrin/Aph2, BACE, Aph1a, and Pen-2 protein.

27. The method of claim 26, wherein the presenilin is presenilin 1.

28. The method of claim 23, wherein the cells are neuronal cells.

29. The method of claim 23, wherein the cells are contacted with the candidate modulator before caspase activation induction.

30. The method of claim 23, wherein the cells are contacted with the candidate modulator after caspase activation induction.

31. The method of claim 23, wherein the caspase activation induces apoptosis.

32. A method for treating or preventing an disorder associated with altered β-secretase and/or γ-secretase processing of substrates, comprising

administering to a subject in need of such treatment an effective amount of a compound that is an inhibitor of the caspase activation-associated stabilization or apoptosis-associated stabilization of a secretase pathway associated protein or secretase pathway associated protein complex.

33. The method of claim 32, wherein the disorder associated with altered β-secretase and/or γ-secretase processing of substrates is an Aβ-accumulation-associated disorder.

34. The method of claim 32, wherein the disorder associated with altered β-secretase and/or γ-secretase processing of substrates is selected from the group consisting of cancer, neurological diseases, immunologic diseases and glycoconjugate metabolism disorders.

35. The method of claim 33, wherein the Aβ-accumulation-associated disorder is selected from the group consisting of Alzheimer's disease, Down's syndrome, cerebrovascular amyloidosis, inclusion body myositis and hereditary inclusion body myopathies, diseases associated with abnormal BACE and/or γ-secretase activity, ischemia, oxidative stress, head

trauma, stroke, hypoglycemia, and any neurodegenerative disorder with increased caspase activation.

36. The method of claim 32, wherein the secretase pathway associated protein is selected from the group consisting of: presenilins, nicastrin/Aph2, BACE, Aph1a, and Pen-2 protein.

37. The method of claim 36, wherein the presenilin is presenilin 1.

38. The method of claim 32, wherein the subject is a human.

39. The method of claim 32, wherein the subject has been diagnosed with Alzheimer's disease or is at risk of developing Alzheimer's disease.

40. The method of claim 32, wherein the compound is linked to a targeting molecule.

41. The method of claim 32, wherein the targeting molecule's target is a neuronal cell.

42. The method of claim 32, wherein the compound is selected from the group consisting of small molecules, polypeptides, and nucleic acids.

43. The method of claim 42, wherein the polypeptide is an antibody or antigen-binding fragment thereof.

44. The method of claim 42, wherein the nucleic acid molecule is selected from the group consisting of: antisense molecules, RNAi molecules, and siRNA molecules.

45. The method of claim 32, wherein the mode of administration is selected from the group consisting of: implantation, mucosal administration, injection , inhalation, and oral administration.

46. The method of claim 33, wherein the compound is administered in combination with an additional drug or therapy for treating an Aβ-accumulation-associated disorder.

47. A method for preparing a drug formulation comprising

identifying a compound that inhibits caspase activation-associated stabilization or apoptosis-associated stabilization of a secretase pathway associated protein or secretase pathway associated protein complex by the method of claim 23 and

formulating the compound for administration to a subject in need of such treatment.

48. The method of claim 47, wherein the drug formulation is used in the treatment of an Aβ-accumulation-associated disorder.

49. The method of claim 48, wherein the Aβ-accumulation-associated disorder is selected from the group consisting of Alzheimer's disease, Down's syndrome, cerebrovascular amyloidosis, inclusion body myositis and hereditary inclusion body myopathies, diseases associated with abnormal BACE and/or γ-secretase activity, ischemia, oxidative stress, head trauma, stroke, hypoglycemia, and any neurodegenerative disorder with increased caspase activation.

50. The method of claim 47, wherein the drug formulation is used in the treatment of a disease or disorder associated with altered β-secretase and/or γ-secretase processing of substrates.

51. The method of claim 50, wherein the disease or disorder is selected from the group consisting of cancer, disorders of cell adhesion, neurological diseases, immunologic diseases, glycoconjugate metabolism disorders and cardiovascular diseases.